

The Association of Urine Arsenic with Prevalent and Incident Chronic Kidney Disease

Evidence from the Strong Heart Study

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Background: Few studies have evaluated associations between low to moderate arsenic levels and chronic kidney disease (CKD). The objective was to evaluate the associations of inorganic arsenic exposure with prevalent and incident CKD in American Indian adults.

Methods: We evaluated the associations of inorganic arsenic exposure with CKD in American Indians who participated in the Strong Heart Study in 3,851 adults ages 45–74 years in a cross-sectional analysis, and 3,119 adults with follow-up data in a prospective analysis. Inorganic arsenic, monomethylarsonate, and dimethylarsinate were measured in urine at baseline. CKD was defined as estimated glomerular filtration rate $\leq 60 \text{ ml/min}/1.73 \text{ m}^2$, kidney transplant or dialysis.

Results: CKD prevalence was 10.3%. The median (IQR) concentration of inorganic plus methylated arsenic species (total arsenic) in

urine was 9.7 (5.8, 15.7) $\mu\text{g/L}$. The adjusted odds ratio (OR; 95% confidence interval) of prevalent CKD for an interquartile range in total arsenic was 0.7 (0.6, 0.8), mostly due to an inverse association with inorganic arsenic (OR: 0.4 [0.3, 0.4]). Monomethylarsonate and dimethylarsinate were positively associated with prevalent CKD after adjustment for inorganic arsenic (OR: 3.8 and 1.8). The adjusted hazard ratio of incident CKD for an IQR in sum of inorganic and methylated arsenic was 1.2 (1.03, 1.41). The corresponding HRs for inorganic arsenic, monomethylarsonate, and dimethylarsinate were 1.0 (0.9, 1.2), 1.2 (1.00, 1.3), and 1.2 (1.0, 1.4).

Conclusions: The inverse association of urine inorganic arsenic with prevalent CKD suggests that kidney disease affects excretion of inorganic arsenic. Arsenic species were positively associated with incident CKD. Studies with repeated measures are needed to further characterize the relation between arsenic and kidney disease development.

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Strong evidence suggests that chronic exposure to arsenic from drinking water¹ and food² is involved in the development of cancer³ and cardiovascular disease.^{4–7} Other health outcomes that have been associated with arsenic exposure include type 2 diabetes,^{8–10} respiratory outcomes,¹¹ and neurodevelopmental and reproductive abnormalities.^{12,13} Fewer epidemiologic studies have evaluated associations between arsenic and chronic kidney disease (CKD).¹⁴ Most studies on arsenic and renal outcomes have focused on proteinuria, showing that high arsenic exposure levels¹⁵ and low arsenic exposure levels¹⁶ are associated with increased albuminuria or proteinuria. In two small studies from Taiwan (Taipei and Central Taiwan), moderate arsenic exposure levels were associated with prevalent CKD, defined as estimated glomerular filtration rate (eGFR) $< 60 \text{ ml/min}/1.73 \text{ m}^2$.^{17,18} In Southeastern Michigan, an ecologic study found a positive association between moderate arsenic concentrations in drinking water (mean 11 $\mu\text{g/L}$) and kidney disease mortality.¹⁹ Little is known, however, about the association between arsenic and CKD at low-moderate levels of exposure.

The objective of this study was to investigate the association between inorganic arsenic exposure, by measuring inorganic (arsenite and arsenate) and methylated (monomethylarsonate and dimethylarsinate) arsenic species in urine, and CKD, defined as eGFR $< 60 \text{ ml/min/1.73 m}^2$, kidney transplant, or dialysis. The sum of inorganic and methylated arsenic species in urine is an established biomarker of recent and ongoing arsenic exposure.²⁰ Because kidney excretion is the primary route for arsenic elimination,²⁰ it is possible that kidney function affects excretion and concentrations of arsenic species in urine.^{21,22} Little is known, however, about how the inorganic and methylated species are excreted in the kidney or if they are affected by GFR. In this study, we evaluated the cross-sectional association of baseline urine arsenic concentrations with prevalent CKD and the prospective association of baseline urine arsenic concentrations with incident CKD among participants free of CKD at baseline. The study was conducted using data from the Strong Heart Study (SHS), a population-based study in American Indian communities from Arizona, Oklahoma, and North and South Dakota.²³ The study population is characterized by low to moderate levels of arsenic exposure through drinking water and food.²⁴ Water arsenic levels in the study areas also include some levels that are higher than the national average as well as the above the current arsenic standard of 10 $\mu\text{g/L}$. In addition, due to the high prevalence of diabetes in the SHS, the participants are at increased risk for developing CKD. In a previous study, we confirmed that the sum of inorganic and methylated arsenic concentrations measured in urine samples collected as baseline was an appropriate biomarker of arsenic exposure over a 10-year period in our study population.²⁴ We have also previously reported that urine arsenic was associated with prevalent albuminuria, with no difference for inorganic or methylated arsenic species.¹⁶

METHODS

Study Population

The SHS was originally funded by the National Heart Lung and Blood Institute to evaluate risk factors for cardiovascular disease in American Indian communities.^{23,24} Men and women 45–74 years of age from 13 tribes and communities in Arizona, Oklahoma, and North and South Dakota were invited to participate.^{23,25} A total of 4,549 participants were recruited (62% response rate). The baseline visits took place between 1989 and 1991, and two follow-up visits took place in 1993–1995 and 1997–1999. The response rates among participants who were alive at the time of the visits were 88% and 89% at visits 2 and 3, respectively.

We used data from 3,974 Strong Health Study participants in whom we have measured urine arsenic at the baseline visit. We excluded 78 participants missing serum creatinine, seven participants missing fasting glucose, and 38 participants missing other variables of interest, leaving 3,851 participants

for the cross-sectional analysis. For the prospective analyses, we further excluded the 395 participants who had CKD (eGFR $\leq 60 \text{ ml/min/1.73 m}^2$, dialysis or kidney transplant) at baseline as well as 331 participants who missed both follow-up visits, leaving 3,119 participants for the prospective analyses. The Strong Health Study protocol and consent form were approved by local institutional review boards, participating tribes and the Indian Health Service. All participants provided informed consent.

Urine Arsenic

Urine collected at baseline was frozen and shipped to the MedStar Health Research Institute, Washington, DC, where it was stored at -80°C . In 2009, up to 1 ml urine sample aliquots were shipped to the Trace Element Laboratory at Graz University, Austria for arsenic analyses. The analytical methods and quality control criteria for the measurement of urine arsenic in the SHS have been described in detail.²⁶ In summary, inorganic arsenic species (arsenite and arsenate, measured together under oxidized conditions), methylated arsenic species (monomethylarsonate and dimethylarsinate), and arsenobetaine plus other arsenic cations were determined by high performance liquid chromatography (HPLC; Agilent 1100, Agilent Technologies, Waldbronn, Germany) coupled to inductively coupled plasma-mass spectrometry (ICP-MS; Agilent 7700x ICPMS). The inter-assay coefficient of variation was below 5% for all arsenic species. The limit of detection was 0.1 $\mu\text{g/L}$ for inorganic arsenic, monomethylarsonate, dimethylarsinate, and arsenobetaine and other arsenic cations. The percentage of samples below the limit of detection was 5.2% for inorganic arsenic, 0.8% for monomethylarsonate, 0.03% for dimethylarsinate, and 2.1% for arsenobetaine and other arsenic cations. Samples below the limit of detection were replaced by the limit of detection divided by the square root of two.

We used the sum of inorganic (arsenite, arsenate) and methylated (monomethylarsonate, dimethylarsinate) arsenic species as our biomarker of inorganic arsenic exposure. In addition, we evaluated inorganic arsenic, monomethylarsonate, and dimethylarsinate separately, as well as arsenobetaine, an arsenical found in seafood that is characterized by very low toxicity. Urine arsenic concentrations ($\mu\text{g/L}$) were divided by urine creatinine concentrations (g/L) to account for urine dilution and expressed in $\mu\text{g/g}$ creatinine. The Spearman's correlation coefficient of inorganic arsenic (arsenate, arsenite) with monomethylarsonate, dimethylarsinate, and arsenobetaine were 0.84, 0.73, and 0.01, respectively.

Plasma and Urine Creatinine Measures

Serum creatinine was measured in fasting venous blood samples by an automated alkaline-picrate rate method (Roche Diagnostics, Basel, Switzerland) using Hitachi 717 platform (Hitachi Ltd., Tokyo, Japan) at all visits.²⁷ eGFR was calculated from creatinine, age, and sex using the Modification of Diet in Renal Disease equation without the ethnicity factor.²⁸

Prevalent CKD was defined as eGFR ≤ 60 ml/min/1.73 m² or presence of kidney transplant or dialysis at baseline.²⁹ Incident CKD was defined as eGFR ≤ 60 ml/min/1.73 m² or presence of kidney transplant or dialysis at either follow-up visits.

Urine creatinine was measured in spot urine samples collected during the baseline visit at the Laboratory of the National Institute of Diabetes and Digestive and Kidney Diseases Epidemiology and Clinical Research Branch, Phoenix, Arizona by an automated alkaline picrate methodology.²³

Other Variables

Information on age, gender, education, smoking status, hypertension medication use, dialysis, and kidney transplant was collected by trained and certified interviewers using standardized questionnaires.²³ Physical exam measures (height, weight, systolic, and diastolic blood pressure) were performed by trained nurses and medical assistants following a standardized protocol. Methods to measure blood pressure, body mass index, fasting glucose, 75 g oral glucose tolerance test, and hemoglobin A1c (HbA1c) have been described.²³ Diabetes was defined as a fasting glucose ≥ 126 mg/dl, a 2-hour post-load plasma glucose ≥ 200 mg/dl, an HbA1c $\geq 6.5\%$, or the use of insulin or an oral hypoglycemic agent.³⁰

Statistical Analyses

Statistical analyses were performed in Stata 11.2 (Stata Corporation, College Station, TX) and R 2.15.2 (R Project, www.r-project.org). Urine arsenic concentrations were right skewed and natural log transformed. Quartiles were generated based on the distribution of urine arsenic concentrations in the overall study sample.

For the cross-sectional analysis, we used logistic regression models to estimate adjusted odds ratios for prevalent CKD by urine arsenic concentrations at baseline. For the prospective analysis, we used Cox proportional hazards models stratified by study location with age as time scale and age at baseline treated as staggered entries. Follow-up time was calculated in years from the date of the baseline visit to the date at the first visit with CKD for participants with incident CKD, and to the date at the last visit for those without incident CKD. This follow-up time was added to the participant's age at the baseline visit. In both logistic and Cox proportional hazards regression models, arsenic concentrations were entered as quartiles (comparing quartiles 2–4 to the lowest quartile), as log-transformed continuous variables (comparing an interquartile range in log-transformed arsenic levels), and as restricted quadratic splines in separate models. *P* values for linear trend were obtained by including a continuous variable with the medians corresponding to each quartile of the arsenic distribution in the regression models.³¹

Models were progressively adjusted. Initially, we adjusted for age (only for logistic models as Cox models already accounted for age), gender, study location (only for logistic models as Cox models were stratified by location), education, body mass index, smoking status, systolic blood

pressure, and hypertension medication (model 2 in prospective models only). Because arsenic has been associated with diabetes prevalence and poor diabetes control in our population,³⁰ we ran additional models adjusting for diabetes and fasting glucose levels (model 3). Results were similar adjusting for HbA1c instead of fasting glucose levels (data not shown). For the prospective association between baseline urine arsenic and incident CKD, because glomerular filtration rate could interfere with arsenic excretion in urine,³² a possibility further supported by our cross-sectional findings especially for inorganic arsenic species, in model 2 we also adjusted for baseline eGFR. This is a common approach to look at CKD progression. In this model, we are evaluating the association between urine arsenic concentrations in urine with incident CKD that are independent of baseline eGFR.

In sensitivity analyses, we accounted for urine dilution adjusting for urine creatinine instead of dividing arsenic by creatinine,³³ and adjusting for specific gravity.³⁴ In analyses adjusted for specific gravity, we also excluded participants with prevalent diabetes and albuminuria. The results of the sensitivity analyses were similar (eTable 1; <http://links.lww.com/EDE/A917>). To account for high mortality rates in the study population,³⁵ we fitted Cox proportional hazards models using the Fine and Gray³⁶ method of handling competing risks with death as the competing event with similar findings (data not shown). Because the exact date of CKD development was unknown and our ascertainment of the study outcome was only available at three visits, we used Poisson regression as an alternative modeling strategy with consistent findings. Using Poisson regression, we also estimated absolute incidence rates across arsenic quartile categories given mean values of covariates (models 3 and 4).

RESULTS

Cross-sectional Findings

The prevalence of CKD at baseline was 10.3% (395/3,851). Participants with prevalent CKD were more likely to be older, female, from Arizona, less educated and former smokers (Table 1). Participants with prevalent CKD were also more likely to have diabetes and higher fasting glucose levels, to use anti-hypertensive medication, and to have higher blood pressure levels. Median (IQR) urine inorganic plus methylated arsenic concentrations were lower in participants with CKD (8.9 [5.2, 14.6] μ g/g) compared with participants without CKD (9.8 [5.9, 15.7] μ g/g). Inorganic arsenic, monomethylarsenate, and dimethylarsinate concentrations were also lower in participants with CKD (Table 1). Arsenobetaine concentrations were similar in participants with and without CKD (Table 2).

The OR for CKD comparing the 75th to 25th percentile of inorganic plus methylated arsenic was 0.7 (0.6, 0.8) after adjusting for sociodemographic and CKD risk factors (Table 3). In separate analyses for each arsenic species, a markedly

TABLE 1. CKD Status by Participant Characteristics at Baseline

Participant Characteristics	Prevalent CKD		Incident CKD	
	No	Yes	No	Yes
Overall no.	3,456	395	2,617	502
Age (years)	54.3 (49, 61.1)	63 (55.8, 68.1)	53.4 (48.5, 60.1)	58.3 (52.5, 64.4)
Sex (%)				
Male	43	23	43	32
Female	57	77	57	68
Study region (%)				
Arizona	34	35	33	39
Oklahoma	33	37	33	33
South Dakota	33	29	34	28
Education (years)	12 (9, 13)	11 (9, 12)	12 (9, 13)	11 (8, 12)
Smoking status (%)				
Never	34	36	32	36
Former	32	40	33	36
Current	35	24	35	28
BMI (kg/m ²)	30.1 (26.6, 34.3)	29.1 (26.1, 33.3)	30.1 (26.6, 34.5)	30.5 (27, 34.3)
Diabetes status (%)				
No	52	36	56	31
Yes	48	64	44	69
Fasting glucose (mg/dl)	115 (110, 174.5)	125 (102, 191)	111 (99, 154)	160.5 (109, 260)
Hypertension medication (%)				
No	79	52	81	71
Yes	21	48	19	29
Systolic BP (mmHg)	124 (113, 136)	134 (119, 153)	123 (113, 135)	130.5 (118, 144)
As concentrations				
iAs + MMA + DMA (µg/g) ^a	9.8 (5.9, 15.7)	8.9 (5.2, 14.6)	9.5 (5.7, 15.4)	11.2 (6.2, 18.2)
iAs	0.8 (0.4, 1.5)	0.4 (0.2, 0.9)	0.8 (0.4, 1.5)	0.8 (0.4, 1.5)
MMA (monomethylarsonate)	1.3 (0.8, 2.2)	1.2 (0.7, 2.2)	1.3 (0.8, 2.2)	1.4 (0.8, 2.5)
DMA (dimethylarsinate)	7.4 (4.5, 12.0)	7.3 (4.0, 11.7)	7.1 (4.4, 11.7)	8.5 (4.8, 13.8)
Arsenobetaine (µg/g)	0.7 (0.4, 1.5)	0.7 (0.4, 2.1)	0.7 (0.4, 1.6)	0.7 (0.4, 1.4)

Data are median (interquartile range) or percentages.

^aSum of inorganic and methylated arsenic species.

BMI indicates body mass index; BP, blood pressure; DMA, dimethylarsinate; iAs, inorganic arsenic; MMA, monomethylarsonate.

strong inverse association was observed for inorganic arsenic (OR for CKD comparing the 75th to 25th percentile was 0.4 (0.3, 0.4). For monomethylarsonate and dimethylarsinate, the inverse associations were weaker and they became positive after adjustment for inorganic arsenic (OR [95% confidence interval {CI}] 3.8 [2.8, 5.1] for monomethylarsonate, and 1.8 [1.4, 2.3] for dimethylarsinate). Urine arsenobetaine was not associated with prevalent CKD. In restricted quadratic spline models, we observed an inverse association between the sum of inorganic and methylated arsenic concentrations and prevalent CKD, which was mostly driven by a strong inverse association with inorganic arsenic (Figure 1). For monomethylarsonate and dimethylarsinate, the inverse association was weaker and it could be related to the correlation between inorganic arsenic and monomethylarsonate and dimethylarsinate species. After adjustment for inorganic arsenic levels, the associations between monomethylarsonate and prevalent CKD, and

dimethylarsinate and prevalent CKD became strongly positive (Figure 1). The inverse association for the sum of inorganic and methylated arsenic species was observed in all participant subgroups evaluated, except in participants younger than 55 years of age (Figure 2).

Modeling eGFR as a continuous variable, higher urine arsenic was associated with higher eGFR levels in all models. After adjustment for all variables in model 3 (eTable 2; <http://links.lww.com/EDE/A918>), an interquartile range in urine arsenic levels was associated with a mean difference of 5.2 (95% CI = 4.1, 6.3) ml/min/1.73 m² for the sum of inorganic and methylated arsenic, 7.9 (6.9, 9.0) ml/min/1.73 m² for inorganic arsenic, 3.0 (1.9, 4.0) ml/min/1.73 m² for monomethylarsonate and 4.8 (3.7, 5.8) ml/min/1.73 m² for dimethylarsinate. After adjusting for inorganic arsenic concentrations, the corresponding mean difference in eGFR was -0.1 (-1.4, 1.1) for monomethylarsonate and 2.5 (1.2, 3.7) ml/min/1.73 m² for dimethylarsinate. In

TABLE 2. Baseline Participant Characteristics by Urine Arsenic Concentrations for Participants Without CKD at Baseline and With At Least One Follow-up Visit (N = 3,119)

Population	Sum of Inorganic and Methylated (µg/g Creatinine)			
	≤5.8	5.8–9.7	9.7–15.6	≥15.6
Number	3,119	772	781	784
Sex				
Male	41	51	40	41
Female	59	49	60	59
Age (years)	54.3 (49.61)	54.4 (48.6 61.1)	54 (48.9, 59.9)	54.7 (49.3, 61.4)
Study location				
Arizona	34	7	26	43
Oklahoma	33	70	38	17
South Dakota	33	23	36	40
Education (years)	12 (9, 13)	12 (11, 14)	12, (10, 14)	11 (8, 12)
BMI (kg/m ²)	30.2 (26.6, 34.5)	30 (27, 34)	30.5 (27.1, 34.9)	30.4 (26.5, 34.6)
Smoking status				
Never	32	31	31	32
Former	34	35	36	33
Current	34	34	34	35
Diabetes				
No	53	64	55	53
Yes	47	36	45	47
Fasting glucose (mg/dl)	115 (100, 176)	108 (99, 131)	111 (98, 152)	113.5 (101, 166)
Hypertension medication				
No	80	78	81	80
Yes	20	22	19	20
Systolic BP (mmHg)	124 (113, 136)	124.5 (115, 135)	123 (112, 134)	124 (113, 138)
eGFR (ml/min/1.73 m ²)	82.4 (75.5, 94.5)	80.4 (71.5, 90.5)	81.8 (74.3, 94.0)	82.4 (76.4, 94.8)
As concentrations				
iAs + MMA + DMA	9.7 (5.8, 15.7)	4.2 (3.4, 5.0)	7.5 (6.6, 8.6)	12.3 (10.9, 13.8)
iAs	0.8 (0.4, 1.5)	0.3 (0.2, 0.4)	0.6 (0.4, 0.8)	1.1 (0.7, 1.4)
MMA	1.3 (0.8, 2.2)	0.6 (0.4, 0.8)	1.0 (0.8, 1.3)	1.7 (1.3, 2.1)
DMA	7.3 (4.4, 12.1)	3.2 (2.6, 3.8)	5.8 (5.1, 6.6)	9.3 (8.2, 10.6)
Urine arsenobetaine	0.7 (0.4, 1.5)	0.6 (0.4, 1.1)	0.7 (0.4, 1.9)	0.7 (0.4, 1.6)

Data are median (interquartile range) or percentages.

BMI indicates body mass index; CKD, chronic kidney disease; DMA, dimethylarsinate; eGFR, glomerular filtration rate; iAs, inorganic arsenic; MMA, monomethylarsonate.

analyses restricted to 3,456 participants without CKD and in 1,356 participants with eGFR ≥ 90 ml/min/1.73 m², the mean difference in eGFR for an interquartile range in inorganic plus methylated arsenic concentrations were 4.4 (3.4, 5.5) ml/min/1.73 m² and 3.4 (1.5, 5.5) ml/min/1.73 m², respectively.

Prospective Findings

The incidence rate of CKD over the study period was 23.5 per 1,000 person-years. Mean follow-up time was 6.86 years. Similar to the cross-sectional analysis, participants who developed CKD were more likely to be older, female, from Arizona, less educated, former smokers, and more likely to have diabetes, use anti-hypertension medication, and have higher blood pressure and higher fasting glucose levels (Table 1). Participants with incident CKD had higher inorganic plus methylated arsenic concentrations in baseline urine (median 11.2

[interquartile range 6.2, 18.2] µg/g creatinine) compared with those without incident CKD (9.5 [5.7, 15.4] µg/g creatinine). Looking at the individual species, baseline monomethylarsonate and dimethylarsinate concentrations were higher in participants with than without incident CKD. Baseline inorganic arsenic species and arsenobetaine concentrations were similar in participants with and without incident CKD.

The hazard ratio (95% CI) for incident CKD comparing the 75th to 25th percentile of inorganic plus methylated arsenic species was 1.2 (1.0, 1.4) after adjusting for all sociodemographic and kidney disease risk factors evaluated (Table 4, model 3). In analyses of the individual species separately, the corresponding hazard ratios were 1.0 (0.9, 1.2) for inorganic arsenic, 1.2 (1.00, 1.3) for monomethylarsonate, and 1.2 (1.0, 1.4) for dimethylarsinate. In flexible dose-response models, a positive prospective association with CKD was observed

TABLE 3. Odds Ratios (95% Confidence Interval) for Prevalent CKD by Quartile of Urine Arsenic Concentrations

Sum of Inorganic and Methylated ($\mu\text{g/g}$)	Cases/Noncases	Model 1	Model 2	Model 3
Quartiles				
≤ 6.9	117/849	1.0 (ref)	1.0 (ref)	—
6.9–11.3	95/865	0.8 (0.6, 1.1)	0.7 (0.5, 1.00)	—
11.3–18.6	94/869	0.8 (0.6, 1.1)	0.6 (0.4, 0.9)	—
≥ 18.6	89/873	0.7 (0.6, 1.0)	0.5 (0.3, 0.7)	—
<i>P</i> trend		0.08	<0.01	—
IQR (15.6 vs. 5.8)	395/3,456	0.8 (0.7, 1.0)	0.7 (0.6, 0.8)	—
Inorganic arsenic ($\mu\text{g/g}$)				
IQR (1.4 vs. 0.3)	395/3,456	0.5 (0.4, 0.5)	0.4 (0.3, 0.4)	—
MMA ($\mu\text{g/g}$)				
IQR (2.2 vs. 0.7)	395/3,456	0.9 (0.8, 1.0)	0.8 (0.7, 1.0)	3.8 (2.8, 5.1)
DMA ($\mu\text{g/g}$)				
IQR (12.0 vs. 4.4)	395/3,456	0.9 (0.8, 1.0)	0.7 (0.6, 0.9)	1.8 (1.4, 2.3)
Arsenobetaine ($\mu\text{g/g}$)				
IQR (1.6 vs. 0.4)	395/3,456	1.0 (0.9, 1.1)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)

Model 1 is unadjusted. Model 2 is adjusted for age and gender, location, education, smoking status, BMI, hypertension medication, SBP, diabetes status, and fasting glucose. Model 3 is additionally adjusted for inorganic arsenic (arsenite, arsenate).

BMI indicates body mass index; BP, blood pressure; DMA, dimethylarsinate; IQR, interquartile range; MMA, monomethylarsonate.

for the sum of inorganic and methylated arsenic species, as well as for monomethylarsonate and especially for dimethylarsinate (Figure 3); by contrast, there was no association for inorganic arsenic. The association between the sum of inorganic and methylated arsenic species and incident CKD was similar across participant characteristics (Figure 2).

DISCUSSION

In this population, primarily from rural communities in the western United States, participants with prevalent CKD had lower concentrations of inorganic plus methylated arsenic species measured in baseline urine, which was mostly explained by a strong inverse association with inorganic arsenic. This finding suggests that glomerular filtration contributes importantly to inorganic arsenic excretion. For urinary monomethylarsonate and dimethylarsinate, we found a positive association with prevalent CKD after adjustment for inorganic urinary arsenic concentrations. Prospectively, baseline urine concentrations of inorganic plus methylated arsenic species were associated with incident CKD. The prospective association between arsenic and CKD remained after adjustment for sociodemographic and CKD risk factors, including baseline eGFR, as well as in most participant subgroups. In analyses of the individual species, the prospective associations remained present for monomethylarsonate and dimethylarsinate but no association was observed with inorganic arsenic concentrations.

The major route of arsenic excretion is through the kidneys.²⁰ Little is known, however, about the precise pathways of excretion for the different arsenic species. In an experiment in dogs, arsenate and arsenite were filtered through the glomeruli and partly reabsorbed by the tubules.³⁷ Arsenic excretion was

decreased in several studies of animals with impaired kidney function. In rabbits, arsenic excretion was reduced in a dose-responsive manner after partial and subtotal nephrectomy.³⁸ None of those animal studies have evaluated the impact of kidney function on the methylated arsenic species.

Few human studies have evaluated arsenic excretion in the presence of impaired kidney function. Dialysis was needed to remove sodium arsenite from blood in two patients with acute sodium arsenite intoxication and acute kidney failure.³⁹ When kidney function recovered, urine total arsenic excretion increased.³⁹ A pharmacologic study of arsenic trioxide treatment in 20 cancer patients with varying kidney function levels found that total arsenic excretion was reduced in patients with impaired kidney function.³² Impaired kidney function also resulted in decreased percentage of total arsenic excreted as arsenite as well as with an increase in plasma monomethylarsonate and dimethylarsinate concentrations.³² However, only in cases of severe renal impairment did the internal dose of arsenite increase.³² In a cancer patient on hemodialysis treated with arsenic trioxide, plasma total arsenic concentration increased in the presence of arsenic trioxide treatment and hemodialysis was not sufficient to reduce plasma arsenic concentrations.⁴⁰

Our cross-sectional findings suggest that chronically reduced glomerular function reduces the excretion of inorganic arsenic but not of monomethylarsonate or dimethylarsinate, or of arsenobetaine. These findings are thus consistent with reverse causation, in which CKD and decreased GFR impair urine arsenic excretion, specifically inorganic arsenic exposure. Decreased inorganic arsenic elimination through the kidneys could result in increased arsenic internal dose and higher risk of

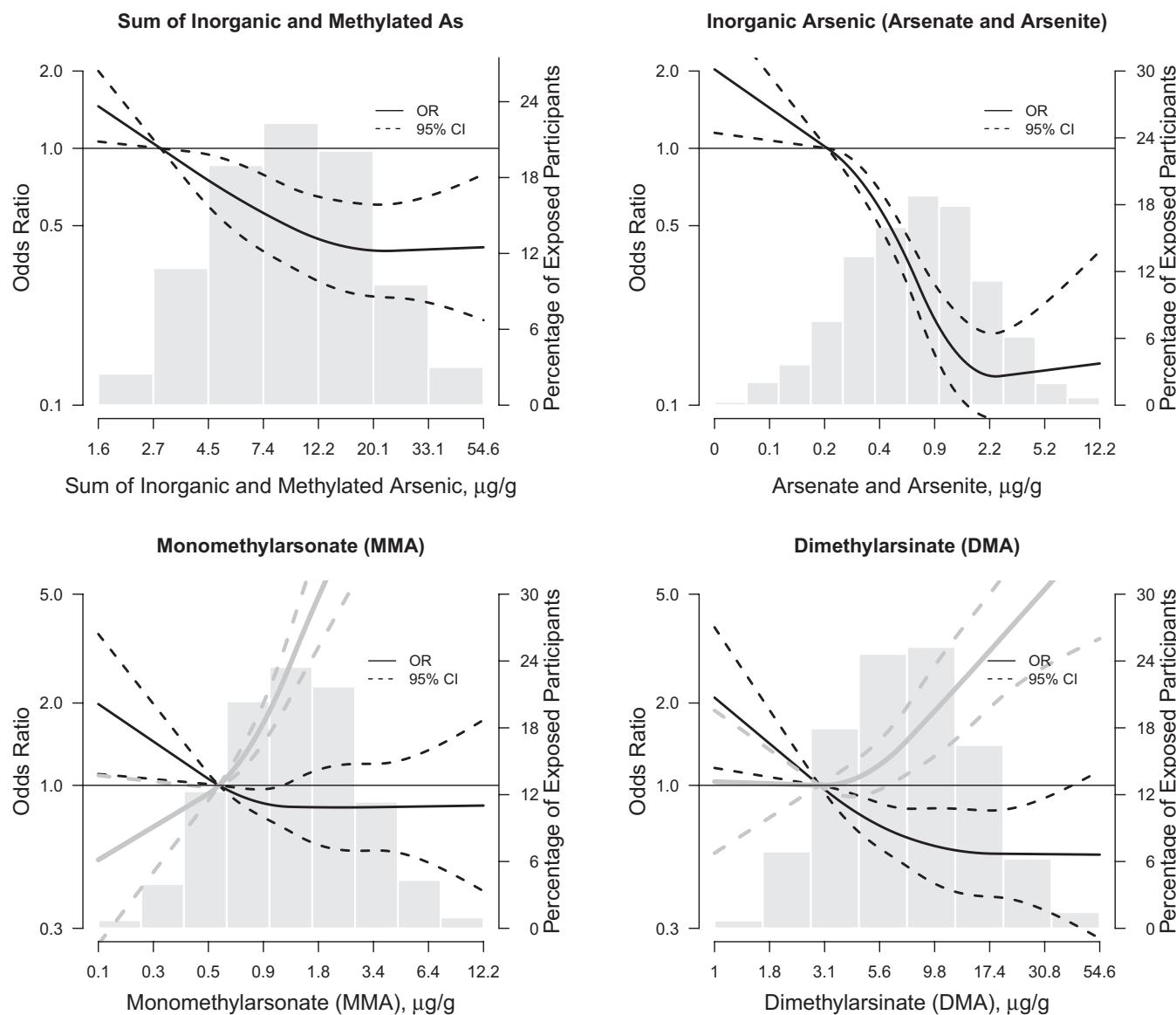


FIGURE 1. Odds ratios for prevalent chronic kidney disease by total arsenic (the sum of inorganic and methylated arsenic species), inorganic arsenic (arsenate and arsenite), monomethylarsonate arsenic, and dimethylarsinate. Black lines (solid lines) Odds ratios and 95% confidence intervals (dashed lines) based on restricted quadratic spline models for log transformed arsenic with three knots and adjusted as in Table 3, model 3. Gray lines (solid lines) are the odds ratios and 95% CI (dashed lines) for monomethylarsonate and dimethylarsinate after adjustment for urine inorganic arsenic levels. The reference was set at the 10th percentile of the urine arsenic biomarker distribution. Odds ratios were adjusted for age (continuous), sex, study region, body mass index (continuous), education, smoking status, diabetes status, hypertensive medication, systolic blood pressure (continuous), and fasting glucose (continuous). For inorganic plus methylated arsenic species the P value for a linear and nonlinear dose-response relations were 0.02 and 0.13, respectively. For inorganic arsenic, the P values for linear and nonlinear dose-response were 0.01 and 0.005. For monomethylarsonate, P values for linear and nonlinear dose-response were, respectively, 0.02 and 0.19 before and 0.10 and 0.003 after adjustment for inorganic arsenic. For dimethylarsinate, P values for linear and nonlinear dose-response were, respectively, 0.01 and 0.14 before and 0.92 and 0.02, after adjustment for inorganic arsenic.

arsenic-related health effects among individuals with CKD. In blood, the longer retention of inorganic arsenic species would allow them to be further methylated. In our study, however, we have no measurements of arsenic species in blood. Several small studies in patients with CKD, including participants on

dialysis, have shown increased arsenic concentrations in serum compared with healthy controls, although levels of urine arsenic were not reported (and urine assessment can be difficult to do in patients on dialysis).^{21,22,41,42} The impact could occur across the range of kidney filtration, rather than just with CKD,

OR and HR of CKD by sum of inorganic and methylated arsenic, stratified by Participant Characteristics

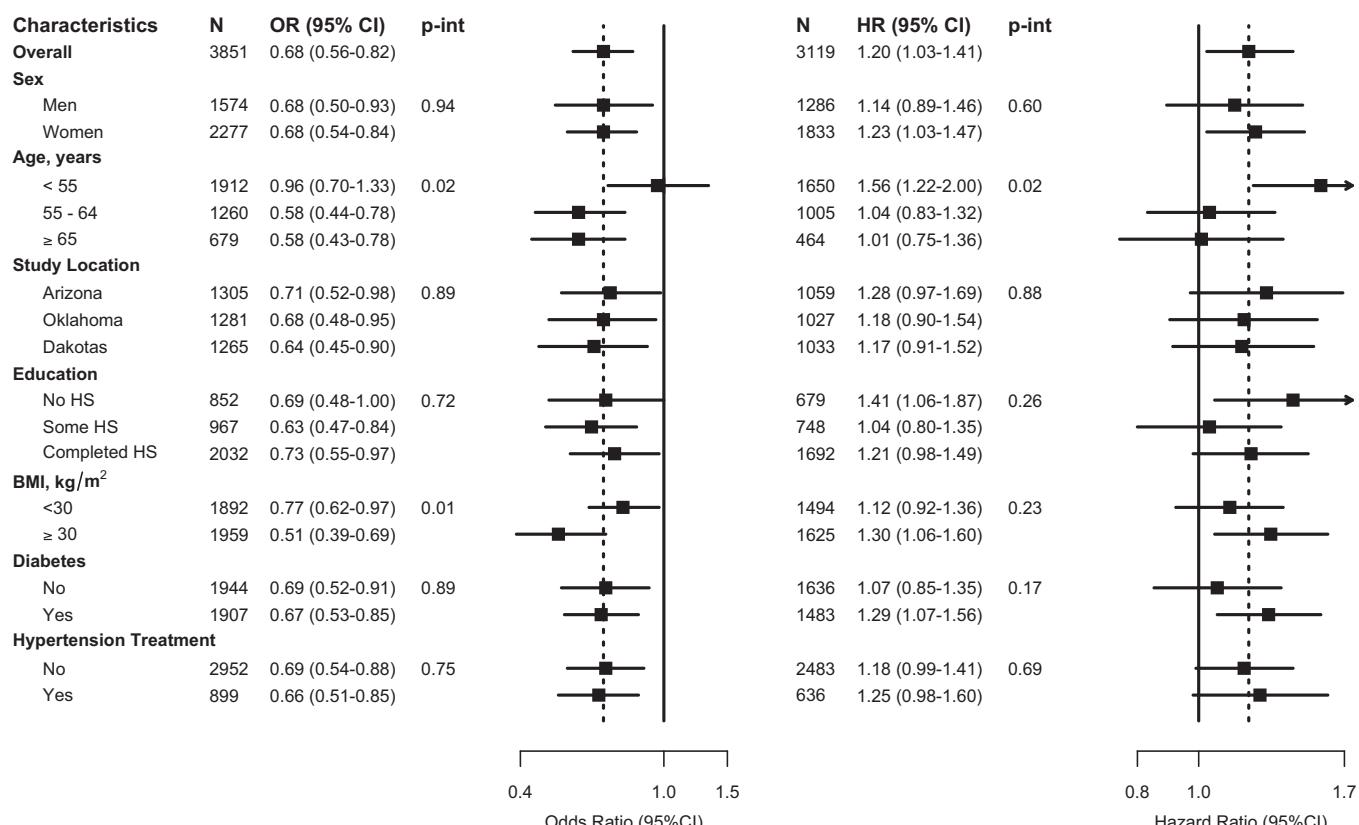


FIGURE 2. OR and HR for chronic kidney disease comparing the 75th to 25th percentile of the sum of inorganic and methylated arsenic species, stratified by participant characteristics. Odds ratios are adjusted for age (years), sex, study region, body mass index (continuous), education, smoking status, diabetes status, hypertensive medication, systolic blood pressure (continuous), and fasting glucose (continuous). Hazard ratios were adjusted for age (continuous), sex, body mass index (continuous), education (continuous), smoking status, diabetes status, hypertensive medication, systolic blood pressure (continuous), baseline eGFR (continuous), and fasting glucose (continuous). Baseline hazard was stratified by study region.

because the association between arsenic, especially inorganic arsenic, and eGFR was present even at eGFR levels $> 90 \text{ ml/min}/1.73 \text{ m}^2$. The marked change in the direction of the association between monomethylarsonate and dimethylarsinate after adjustment for inorganic arsenic needs to be interpreted cautiously. Although our analysis can support that the evidence that methylated species are a risk factor for CKD and the result is consistent with the prospective analyses, we cannot rule out that the moderate to strong correlation between the inorganic and methylated arsenic species results in an artifact.

A second possible explanation for the observed inverse association between arsenic and prevalent CKD that becomes positive with incident CKD is hyperfiltration. Hyperfiltration is the presence of an elevated GFR in the early stages of kidney disease before a decline in GFR in later stages of kidney disease. Hyperfiltration is well established in the early stages of kidney diseases associated with diabetes and obesity,⁴³ and with sickle cell disease.⁴⁴ It has also been proposed for environmental nephrotoxicants such as lead.^{45,46} A caveat to this hypothesis is that little is known about whether arsenic could

induce hyperfiltration; as no human or animal studies, to the best of our knowledge, have evaluated the possible role of arsenic exposure in hyperfiltration.

Few experimental studies have evaluated the role of arsenic in kidney disease development. In vitro and animal studies support the role of high arsenic exposure levels in kidney damage,^{47,48} although the relevance of those studies is unclear as arsenic concentrations were very high. For instance, subcytotoxic but still high arsenite (10 $\mu\text{mol/L}$) and arsenate (25 $\mu\text{mol/L}$) concentrations inhibited mitochondrial metabolism in proximal tubule cells.⁴⁹ Arsenic can also influence inflammatory processes in in vitro models, as measured by increased IL-6 and IL-8 expression,⁵⁰ and reactive oxygen species pathways.⁵¹ In rodents exposed to 5 mg/kg arsenic trioxide, markers of kidney function (serum urea nitrogen and serum creatinine), markers of kidney injury (urine N-acetyl- β -D-glucosaminidase), and markers of reactive oxygen species increased in arsenic trioxide-treated kidney tissue compared with controls.⁵² Through these mechanisms, arsenic could also play a role in arsenic-related kidney damage.⁵³

TABLE 4. Hazard Ratios (95% Confidence Interval) for Incident CKD by Urine Arsenic Concentrations

Sum of Inorganic and Methylated ($\mu\text{g/g}$)	Cases/Noncases	Model 1	Model 2	Model 3
Quartiles				
≤ 5.7	109/663	1.0 (ref)	1.0 (ref)	1.0 (ref)
5.8–9.7	110/671	1.0 (0.8, 1.4)	1.1 (0.8, 1.4)	1.1 (0.8, 1.4)
9.7–15.6	128/656	1.2 (0.9, 1.5)	1.2 (0.9, 1.7)	1.2 (0.9, 1.6)
≥ 15.6	155/627	1.4 (1.0, 1.9)	1.6 (1.2, 2.2)	1.3 (0.9, 1.8)
<i>P</i> trend		0.01	<0.01	0.12
IQR (15.6 vs. 5.8)	502/2,617	1.2 (1.1, 1.4)	1.3 (1.1, 1.5)	1.2 (1.0, 1.4)
Inorganic arsenic ($\mu\text{g/g}$)				
IQR (1.5 vs. 0.4)	502/2,617	0.9 (0.8, 1.1)	1.1 (0.9, 1.3)	1.0 (0.9, 1.2)
MMA ($\mu\text{g/g}$)				
IQR (2.2 vs. 0.8)	502/2,617	1.1 (0.9, 1.2)	1.2 (1.0, 1.4)	1.2 (1.0, 1.3)
DMA ($\mu\text{g/g}$)				
IQR (12.1 vs. 4.4)	502/2,617	1.3 (1.1, 1.5)	1.3 (1.2, 1.6)	1.2 (1.0, 1.4)
Arsenobetaine ($\mu\text{g/g}$)				
IQR (1.5 vs. 0.4)	502/2,617	1.1 (0.9, 1.2)	1.0 (0.9, 1.1)	1.1 (1.0, 1.2)

Model 1 is unadjusted. Model 2 is adjusted for age and gender, location, education, smoking status, BMI, hypertension medication, SBP, and baseline eGFR. Model 3 is additionally adjusted for diabetes status and fasting glucose.

BMI indicates body mass index; BP, blood pressure; CKD, chronic kidney disease; DMA, dimethylarsinate; IQR, interquartile range; MMA, monomethylarsonate.

In human populations, ecologic studies estimating standardized mortality ratios (SMRs) have found associations between high arsenic levels in drinking water and kidney disease mortality including evidence from Antofagasta, Chile⁵⁴ and Southwestern Taiwan.⁵⁵ At lower levels of arsenic exposure, an ecological study in Southeastern Michigan (mean water arsenic 11 $\mu\text{g/L}$) found elevated kidney disease mortality compared with the rest of Michigan in both men (SMR: 1.28, 95% CI = 1.15, 1.42) and women (SMR: 1.38, 95% CI = 1.25, 1.52).¹⁹ In another ecological study of residents of Millard County in Utah (median arsenic concentrations ranging from 14 to 166 $\mu\text{g/L}$ in selected towns), the SMR for mortality due to nephritis and nephrosis was increased among men (SMR: 1.72, 95% CI = 1.13, 2.50), but nonincreased among women (SMR: 1.21, 95% CI = 0.66, 2.03).⁵⁶ In a systematic review, the overall pooled SMR was 1.29 (95% CI = 1.10, 1.51).¹⁴ Our prospective results are consistent with those ecologic findings.

The major strengths of our study were the availability of arsenic speciation and the ability to compare cross-sectional and prospective findings. The laboratory techniques for assessing urine arsenic are state-of-the art and highly sensitive, resulting in few participants below the limit of detection (less than 6% for inorganic arsenic).²⁶ The speciation of arsenic in urine allowed us to distinguish exposure to inorganic arsenic, confirm that organic arsenic from seafood was low, and evaluate different associations with different species. The protocols for recruitment, interviews, examinations, and collection and storage of biological samples were highly standardized. The losses to follow-up were low and we had little missing data.

Our study has several limitations. First, eGFR levels were only measured at baseline and two follow-up visits. Therefore,

the exact date of CKD development was unknown. Second, as the direct determination of GFR is not feasible in large population studies, we estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration equation for baseline and cross-sectional analyses and the Modification of Diet in Renal Disease equation for follow-up assessment of incident CKD. The Modification of Diet in Renal Disease equation was developed in individuals with kidney disease, and as a result, the equation has greater imprecision and underestimates GFR in individuals with $\text{GFR} > 60 \text{ ml/min/1.73 m}^2$.⁵⁷ In the SHS, the isotope dilution mass spectrometry-calibrated serum creatinine measures required for the CKD-EPI were only available at baseline, so that it could not be used for outcome assessment. Third, we used spot urine samples to measure arsenic exposure, which must be adjusted for urine dilution. Our main analysis divided by urine creatinine to account for urine dilution. In sensitivity analyses, we adjusted for specific gravity, with consistent findings (eTable S1; <http://links.lww.com/EDE/A917>). Also, we could not evaluate arsenite and arsenate separately, as both species were measured simultaneously under oxidized conditions.²⁶ Fourth, our study population has a high burden of obesity, diabetes, and CKD. Generalization to a population with a different disease profile may be limited. However, the prospective associations remained after adjustment for CKD risk factors, including diabetes and fasting glucose levels, which have been associated with arsenic in the SHS population³⁰ and other studies in American Indians⁸ and Northern Mexicans,⁵⁸ and could be potential mediators of the association between arsenic and CKD. Finally, competing risks such as censoring by death could be a problem in this study population, characterized by a high burden of disease.³⁵ Our sensitivity analyses using the

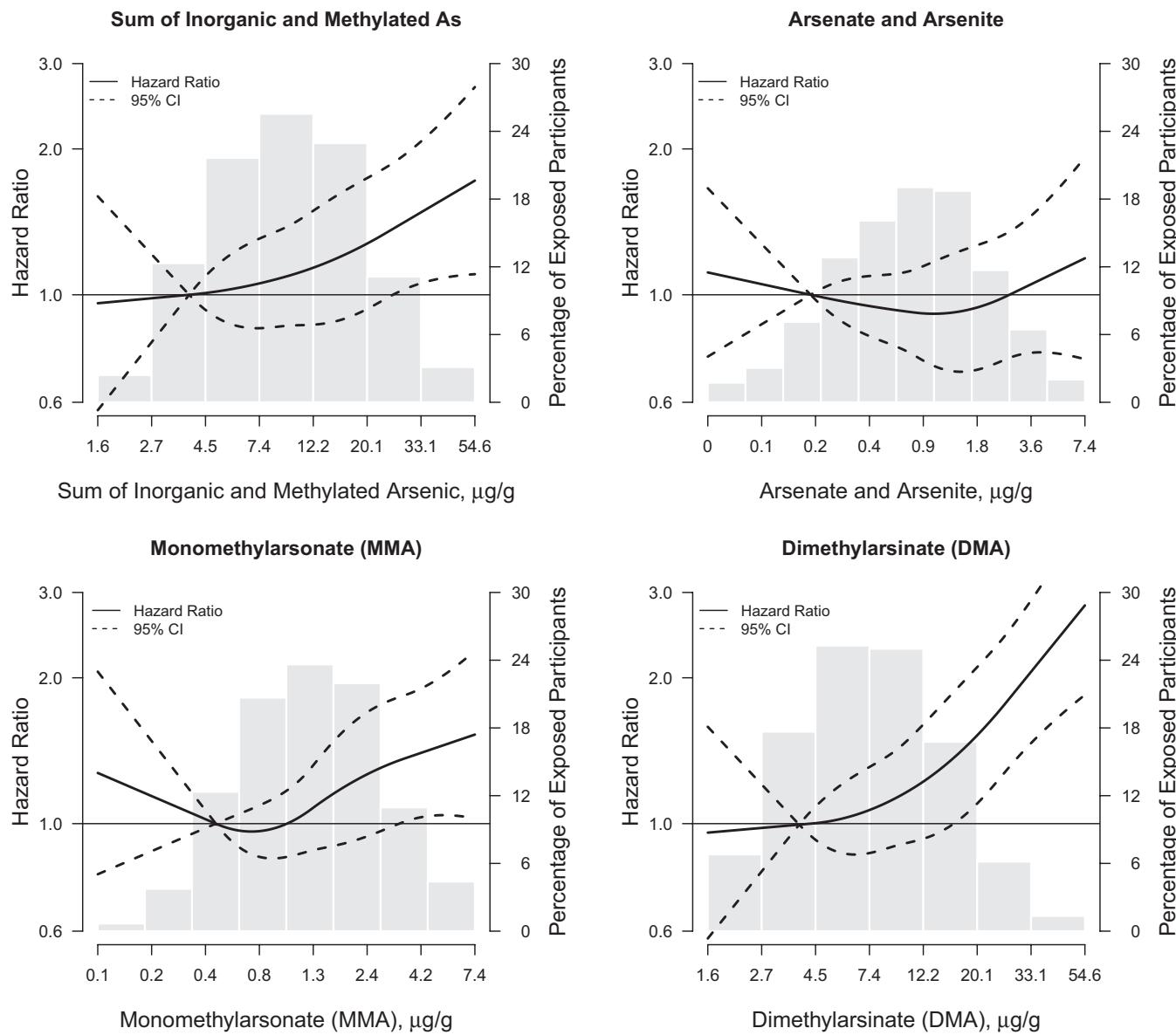


FIGURE 3. Hazard ratio for incident CKD by the sum of inorganic and methylated arsenic species. Lines Hazard ratios (solid lines) and 95% confidence intervals (dashed lines) based on restricted quadratic spline models for log transformed arsenic with three knots. The reference was set at the 10th percentile of the urine arsenic biomarker distribution. Hazard ratios were adjusted for age (continuous), sex, body mass index (continuous), education (continuous), smoking status, diabetes status, hypertensive medication, systolic blood pressure (continuous), eGFR (continuous), and fasting glucose (continuous). Baseline hazard was stratified by study region. The P value for linear dose-response relation for the sum of inorganic and methylated species was 0.80 and the P value for a nonlinear dose-response was 0.69. The P value for a linear dose-response relation for inorganic arsenic was 0.31 and the P value for a nonlinear dose-response was 0.47. For monomethylarsonate, the P value for a linear dose-response relation was 0.32 and 0.23 for a nonlinear dose-response relation. For dimethylarsinate, the P value for a linear dose-response relation was 0.91 and 0.61 for a nonlinear dose-response relation.

Fine and Gray method to handle competing risks resulted in similar findings.

CONCLUSIONS

Prevalent CKD was inversely associated with the sum of inorganic and methylated arsenic concentrations in urine, and

particularly with inorganic arsenic concentrations. These cross-sectional findings suggest that kidney disease is associated with the excretion of inorganic arsenic species. Prospectively, inorganic plus methylated urine arsenic concentrations, especially monomethylarsonate and dimethylarsinate concentrations, were positively associated with incident CKD. These findings could

support the hypothesis that arsenic is a kidney disease risk factor. Studies with repeated measures of arsenic species in urine and blood as well as renal dysfunction end points are needed to further characterize the association among arsenic exposure, excretion of the arsenic species, and CKD development.

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